Proceedings of the 9th World Congress on Recent Advances in Nanotechnology (RAN 2024)
London, United Kingdom –April 8 – 10, 2024
Paper No. NDDTE 130
DOI: 10.11159/nddte24.130

Nanoparticle's Shape Is the Game-Changer for a Customized Delivery through Tunneling Nanotubes among Glioblastoma Cells

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Extended Abstract

Over the past decade, increasing evidence suggested that cells are capable of establishing long distance communication routes with different function defined as Tunneling Nanotubes (TNTs).

TNTs are thin, dynamic, long membrane protrusions that allow the intercellular exchanges of signal clues, molecules, organelles and pathogens. The presence of TNTs has been observed in several types of cancer, glioblastoma (GBM) included, where they emerge to steer a more malignant phenotype [1]. GBM is the most common malignant tumour of Central Nervous System (CNS), representing about 82% of cases of all malignant gliomas [2]. An innovative strategy that could represent a potential therapeutic approach is the targeting of tumour cells communication. Therefore, we are studying TNTs in GBM, to deepen both their structural and *genesis* features in order to exploit them to improve the intercellular distribution of nanomedicines in close and far away cells, thus reaching isolated tumour niches that are hardly targeted by simple drug diffusion in the brain parenchyma.

Until now, different types of nanoparticles have been identified within TNTs. Very little is known about the role of fundamental physical parameters of nanoparticles such as size, charge, shape in determining their penetration across the BBB and their transfer between cells by TNTs.

Considering that, TNTs thickness is in the range of 0.2-1 μm, it can be speculated that the size should not be a critical parameter while positively charged NPs could trigger the formation of TNTs due to a higher toxicity compared to those that are negatively charged. At the best of our knowledge, no data are available about the effect of NPs shape on the transfer efficiency between TNTs.

For this purpose, spherical, discoidal and deformable nanoparticles were synthetized in order to evaluate if the nanoparticles shape could influence their ability to be transferred *via* TNTs. These nanoparticles were evaluated in 2D and 3D *in vitro* models composed of human GBM cells, carrying the EGFRvIII mutation and resistant to temozolomide [3].

The results showed that a single GBM cell is able to form more than one TNT and that TNTs are dynamic and transient structures. They can be actin or actin and α-tubulin positive, they can have a length between 20-100 μm with a thickness of 200-600 nm. Moreover, GBM TNTs are efficient in allowing the intercellular transport of the three different types of nanoparticles tested, in a bidirectional vesicles-free way. Nanoparticles were followed inside TNTs and their average and maximum velocity was evaluated. Moreover, through a co-culture assay it has been demonstrated that the shape affects the efficiency of the nanoparticles exchange *via* TNTs because the discoidal ones were those transferred most efficiently, in comparison to the other two nanoparticles.

Additionally, we address the presence of the TNTs in 3D-tumour organoids. GBM cells grown in a 3D scaffold better recapitulate the features of patient-derived cells, in comparison to 2D culture conditions. Results confirmed the localization of nanoparticles in the TNTs.

Finally, the blood-brain barrier permeability of nanoparticles was measured *in vitro* in a transwell system and the results showed that discoidal nanoparticles displayed the highest endothelial permeability (~ 1.4x10-5 cm/min) with respect to the other nanoparticles tested.

These results make TNTs promising tools for the delivery of drug-loaded discoidal nanoparticles between close and distant cells. This potential is relevant because communication modalities play key roles in driving GBM therapy resistance. Since the formation of TNTs occur also in other type of tumours, these findings can be also exploited in other context.

References

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